

One year mortality outcomes from the ACTA trial of cryptococcal meningitis treatment in Malawi

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Abstract

In Malawi, 236 participants from the ACTA cryptococcal meningitis treatment trial were followed-up for 12 months. The trial outcomes reported at 10 weeks were sustained to 1 year. One-week amphotericinB plus flucytosine was associated with the lowest 1 year mortality (27.5% [95%CI: 16.3 to 44.1]).

Key words: Cryptococcal meningitis, treatment, long-term follow-up, Malawi, HIV

Background

Mortality from cryptococcal meningitis (CM) remains unacceptably high in Sub-Saharan Africa [1]. The most widely used treatment, fluconazole (FLU) monotherapy is associated with mortality of 50-60% at 10 weeks and >70% at 1 year [2-5]. The Advancing Cryptococcal meningitis Treatment for Africa (ACTA) trial [6] recently tested new induction treatment strategies against the 2010 recommended standard of 2 weeks AmB-based induction treatment [7]. The new treatment strategies were FLU plus flucytosine(5FC) given orally for 2 weeks, and AmB given for 1 week with either FLU or 5FC. The aim was to improve outcomes in cryptococcal meningitis with regimens that could be sustained in resource-limited settings. At 10 weeks of follow-up, results from the trial showed that the oral combination was non-inferior to 2 weeks AmB+5FC. One week AmB+5FC was associated with the lowest mortality overall. While 10 week mortality is the most commonly used endpoint in cryptococcal meningitis trials, there is less controlled data on longer term outcomes. Herein, we report the results at 12 month of follow-up for participants enrolled at 2 centres in Malawi, comprising a subset of all those enrolled in the trial.

Methods

ACTA was a large open label, phase III, randomised non-inferiority, multi-centre trial, in which 721 patients with HIV-associated cryptococcal meningitis from centres in Malawi, Zambia, Tanzania and Cameroon were randomised to three strategies: oral FLU+5FC for 2 weeks, 1 week AmB, and standard 2 weeks AmB; and those in the AmB arms were further randomised to 5FC or FLU in a 1:1 ratio, as the partner drug given with AmB. Outcomes at 10 weeks of antifungal therapy have been reported [6]. In this pre-planned sub-study of the ACTA trial, participants at 2 centers in Malawi

(Kamuzu Central Hospital, Lilongwe and Zomba Central Hospital; representing almost 1/3 of patients from the main trial and with sufficient resources for appropriate and complete follow-up, were followed up for 12 months, with primary endpoints of all-cause mortality at 6 and 12 months.

Data Collection

Trained study personnel (nurse or clinician) collected data using a structured questionnaire and record review. Face-to-face interviews were conducted at 6 and 12 months post-trial entry. If face-to-face interviews were not possible patients were followed up by telephone (see supplementary appendix for details)..

Statistical analysis.

Stata 14.2 (StataCorp LP, College Station, TX, USA) was used for statistical analysis. All-cause mortality at 10 weeks, 6 months and 1 year was compared between the treatment groups using log-rank tests. Kaplan–Meier plots were constructed, and Cox regression models with treatment as a predictor were used to derive hazard ratios and 95% confidence intervals (CI). The analyses were also adjusted for pre-specified baseline covariates: site, age, sex, Glasgow Coma Scale (GCS), CD4+ cell count, cerebrospinal fluid (CSF) fungal count and ART status, and performed on both intention-to-treat (ITT) and per-protocol populations; as in the main trial analysis [6]. Analyses were undertaken to explore the consistency of the main trial results over time.

Ethics.

The ACTA trial protocol was approved by the London School of Hygiene and Tropical Medicine Research Ethics Committee and by the national ethics and

regulatory bodies in each country [6]. Ethical approvals for this sub-study were obtained from the National Health Sciences Research Committee of Malawi (NHRSC) and University of North Carolina School of Medicine Institutional Review Board. Written informed consent was obtained from all participants or their next of kin.

Results

From January 2013 to November 2016, 236 patients were randomised; 186 patients in Lilongwe and 50 patients in Zomba (Supplementary Figure 1). Of these, 12 patients were excluded from all analyses, as in the main trial [6]: 4 did not meet inclusion criteria (2 had previous CM and 2 were CM negative), 7 met pre-defined late exclusion criteria, and 1 immediately withdrew consent. Thus, 224 patients formed the intention-to-treat (ITT) population. In total, 144 patients were alive at 10 weeks and all were followed up at 1 year, with no losses to follow-up.

Baseline characteristics were consistent with those of the trial as a whole (Supplementary Tables 1, 3, 5). In total, 63% (141/224) of patients reported that they were taking, or had previously taken, ART. Patients who said that they had never taken ART started ART at a median of 28 days (IQR: 27-32) after randomization. Of the 123 participants that survived to 1 year, ART adherence data was available for 113 participants: 109 participants (96.5%) were reportedly fully adherent. Of the 21 participants that died between 10 weeks and 1 year 61.9% (13/21) were reportedly fully adherent with no obvious imbalance of non-adherent participants between the arms.

Mortality at 10 weeks followed the main trial results. Supplementary tables 4 and 6 show results for the comparison of the 3 treatment strategies and for the comparison of the partner drug, FLU or 5FC, given with AmB. Figure 1A and B, and supplementary Table 2 show the results for the comparison between the 5 treatment arms.

Overall mortality was 35.7% at 10 weeks (95%CI: 29.4-42.4, n=80/224), 41.1% at 6 months (95% CI: 35.0-47.8, n=92/224), and 45.1% at 1 year (95%CI: 38.9-51.8, n=101/224). . Thus, of those surviving to 10 weeks, 85% (123/144) survived to 1 year. Results at 10 weeks were sustained to 6 and 12 months. In particular, results for the 5 treatment arms are shown in Figure 1A (adjusted analyses with 2 weeks AmB+5FC as comparator; results with 1 week AmB+5FC as comparator shown in supplementary Table2) and Figure1B and C. One week AmB+5FC was associated with a 12 month mortality of 27.5% (95%CI: 16.3-44.1) which was not statistically significantly different from that in the other arms. Hazard ratios for mortality, comparing 2 weeks AmB+5FC with other treatment arms were similar at 6 and 12 months to those at 10 weeks; for example, comparing 2 weeks AmB+5FC with 1 week AmB+5FC, hazard ratios (95%CI) were 1.91 (0.83-4.39), 1.84 (0.86-3.95) and 1.90 (0.88-4.08) at 10 weeks, 6 months and 12 months, respectively (Supplementary Table 2).

These hazard ratios are similar to those for this comparison in the trial as a whole at 10 weeks (HR [95%CI]: 1.79, [1.10-2.89] [6]). Results at all time points were similar for adjusted and unadjusted and for ITT and per protocol analyses. When mortality between 10 weeks and 1 year was analysed, there was no difference between

groups, as expected, although 1 week AmB+5FC had lowest proportion of late deaths, 2/31 (6%).

Comparing AmB partner drugs, the hazard of death was significantly lower for participants administered 5FC compared to those taking FLU at all time points (1 year: HR: 0.56, 95%CI: 0.34-0.91, log-rank p-value: 0.02) (Supplementary Table 6).

There was no evidence for a difference in mortality at 12 months between participants who had previously been exposed to ART (43.4%) and unexposed participants (48.2%) (HR: 0.89, 95%CI: 0.60-1.33, log rank p-value: 0.58) (Supplementary Figure 2), though numbers are low.

Discussion

Drug treatment effects observed at 10 weeks were sustained at 12 months, with remarkably low mortality (27.5%) evident in the 1-week AmB+5FC arm. This sub-study, with complete follow-up of 224 participants to 1 year post induction therapy, extends the results seen at 10 weeks in the ACTA trial overall. The long term benefit seen with 1 week AmB+5FC supports updated WHO guidelines recommending this regimen as first-line induction therapy, and underlines the need for rapid wide access to 5FC [8, 9].

The results also confirm that, after 10 weeks, mortality rates decrease, with a general flattening out of survival curves, in the context of effective anti-fungal therapy and appropriately timed ART (i.e. 4 weeks after the start of antifungal therapy). The few long term follow-up data that are available in the context of timely ART initiation for all patients are consistent with our study in this regard [10, 11]. The long term

mortality curves in all the regimens tested here contrast with studies using fluconazole monotherapy, in which progressively increasing mortality resulted in mortality at 12 months of over 75% [4], further emphasising the benefit of currently recommended regimens over fluconazole monotherapy. Given the relatively low mortality between 10 weeks and 1 year, our results also suggest that life threatening CM-IRIS reactions are uncommon or can usually be managed, with awareness and appropriate investigation and treatment [12].

No differences in long term survival were detected between participants previously exposed to ART and ART unexposed participants. Further work is needed to separate out, within the ART exposed group, those with unmasking CM-IRIS and those who have failed ART due to adherence or resistance issues. Our results underline that all these patients can have a good long term prognosis if they survive meningitis. Thus, continued efforts are needed to target and support patients with advanced HIV disease, as recently emphasised by WHO and others [8, 9]. Lastly, significantly lower mortality was observed for participants administered 5FC compared to those taking FLU as a partner drug with AmB, at all time points underlining the urgent need to make 5FC readily available for patients with CM.

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Figure 1. Panel A, Time to event outcomes by 5 treatment arms (Intention-to-treat, adjusted analysis; N=224). Panels B and C show the cumulative all-cause mortality by 5 treatment arms up to 10 weeks (Panel B) and 1 year (Panel C) post randomization.

*log rank p-value for the unadjusted analysis

